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**Filed** : **December 2, 2003**

## **AMENDMENTS TO THE SPECIFICATION**

**Please replace the paragraphs beginning on page 4, line 12, with the following rewritten paragraphs:**

**[0009]** Embodiments of the invention relate to human monoclonal antibodies that specifically bind to Tumor Necrosis Factor- $\alpha$  and have a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Ser Tyr Asp Met His” (SEQ ID NO: 321). Antibodies described herein can also include a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly” (SEQ ID NO: 322), a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val” (SEQ ID NO: 323), a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 70, and a heavy chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 74.

**[0010]** Further embodiments include human monoclonal antibodies having a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly” (SEQ ID NO: 324). Antibodies herein can also include a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Ala Ala Ser Thr Leu Gln Ser” (SEQ ID NO: 325), a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Leu Gln His Lys Ser Tyr Pro Leu Thr” (SEQ ID NO: 326), a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 72.

**[0011]** In other embodiments, the invention provides human monoclonal antibodies that specifically bind to Tumor Necrosis Factor- $\alpha$  and comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Ala Ser Gln Gly Ile Arg Ile Asp Leu Gly” (SEQ ID NO: 324), a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Ala Ala Ser Thr Leu Gln Ser” (SEQ ID NO: 325), and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Leu Gln His Lys Ser Tyr Pro Leu Thr” (SEQ ID NO: 326).

**[0012]** Still further embodiments include human monoclonal antibodies having a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of

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“Ser Tyr Asp Met His” (SEQ ID NO: 321), a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Val Ile Trp Ser Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys Gly” (SEQ ID NO: 322), and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Glu Val Glu Ser Ala Met Gly Gly Phe Tyr Tyr Asn Gly Met Asp Val” (SEQ ID NO: 323).

**Please replace the paragraphs beginning on page 5, line 24, with the following rewritten paragraphs:**

**[0015]** In other embodiments, the invention provides human monoclonal antibodies that specifically bind to Tumor Necrosis Factor- $\alpha$  and include a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Asn Tyr Met Ser” (SEQ ID NO: 327). Antibodies can further include a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly” (SEQ ID NO: 328), a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Gly Glu Gly Gly Phe Asp Tyr” (SEQ ID NO: 329), and a heavy chain amino acid having the amino acid sequence shown in SEQ ID NO: 50.

**[0016]** In further embodiments of the invention, human monoclonal antibodies can include a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala” (SEQ ID NO: 330), a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Gly Ala Ser Ile Arg Ala Thr” (SEQ ID NO: 331), a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Gln Gln Tyr Asn Tyr Trp Trp Thr” (SEQ ID NO: 332), and a light chain amino acid comprising the amino acid sequence shown in SEQ ID NO: 52.

**[0017]** In still further embodiments, the invention includes human monoclonal antibodies that specifically bind to Tumor Necrosis Factor- $\alpha$  and have a light chain complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala” (SEQ ID NO: 330), a light chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Gly Ala Ser Ile Arg Ala Thr” (SEQ ID NO: 331), a light chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Gln Gln Tyr Asn Tyr Trp Trp Thr” (SEQ ID NO: 332), a heavy chain

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complementarity determining region 1 (CDR1) having an amino acid sequence of “Arg Asn Tyr Met Ser” (SEQ ID NO: 327), a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence of “Val Ile Tyr Ser Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly” (SEQ ID NO: 328), and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence of “Gly Glu Gly Gly Phe Asp Tyr” (SEQ ID NO: 329).

**Please replace the following table heading for Table 31 on page 89 with the following rewritten table heading:**

Table 31. Xenomax XENOMAX® Heavy Chain Analysis

**Please replace the following table heading for Table 32 on page 91 with the following rewritten table heading:**

Table 32. Xenomax XENOMAX® Light Chain Analysis

**Please replace the following paragraph beginning on page 2, line 18, with the following rewritten paragraph:**

[0003] TNF $\alpha$  has been demonstrated to be involved in infectious diseases, immune disorders, autoimmune pathologies, graft vs host disease (GVHD), neoplasia/cancer and cancer-associated cachexia. *See*, Feldman M., 2002 *Nat. Rev. Immunol.*, 2:364. In particular, TNF $\alpha$  levels are dramatically induced in gram negative sepsis sepsis, endotoxic shock (*See*, Michie et al., 1989 *Br. J. Surg.* 76:670) Crohn’s disease, and rheumatoid arthritis. The implications of TNF $\alpha$  in such a wide variety of indications highlights the importance of developing specific biological therapeutics targeting this inflammatory cytokine.

**Please replace the following paragraph beginning on page 16, line 1, with the following rewritten paragraph:**

[0064] In addition, embodiments of the invention provide for using these antibodies as a diagnostic tool or for treatment of a disease. For example, embodiments of the invention provide methods and antibodies for inhibiting expression of TNF $\alpha$  associated with infectious

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diseases, immune disorders, autoimmune pathologies, graft vs. host disease (GVHD), neoplasia, cancer associated cachexia, gram negative ~~sepsis~~ sepsis, endotoxic shock, Crohn's disease, and rheumatoid arthritis. Preferably, the antibodies are used to treat cancers, such as breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer, as well as other inflammatory conditions, including, but not limited to, rheumatoid arthritis, glomerulonephritis, atherosclerosis, psoriasis, organ transplants, restenosis and autoimmune diseases. In association with such treatment, articles of manufacture including antibodies as described herein are provided. Additionally, an assay kit having antibodies as described herein is provided to screen for tumors and inflammatory conditions.

**Please replace the following paragraph beginning on page 81, line 1, with the following rewritten paragraph:**

[0221] The binding affinity of 299v2 for cynomolgus macaque TNF $\alpha$  was also measured, since this antibody had been found capable of binding monkey TNF $\alpha$  in an ELISA. The KinExA KinExA<sup>®</sup> method was also used to measure the K<sub>d</sub> describing this binding affinity. 299v2 bound to monkey TNF $\alpha$  with an affinity of 626 pM, considering TNF $\alpha$  as a monomer, which is therefore approximately 200 times lower than the affinity for human TNF $\alpha$ .